DETAILED ACTION

Claims 1, 2, 4-7 and 9-25 are pending in the application.

Receipt is acknowledged of the amendment filed June 9, 2011, which has been entered in the file.

Information Disclosure Statement

The information disclosure statement(s) (IDS) submitted on May 17, 2011 and June 9, 2011 has(have) been considered. The submission(s) is(are) in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement(s) is(are) being considered by the examiner.

Claim Rejections - 35 USC § 112, New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 to 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no antecedent basis in the specification for a method of "treating a refractile mammalian cancer cell" or the specific cancer cells set forth in claim 13. Page

17 paragraph [0051] of the specification states that salinosporamides are excellent candidates for use in the treatment of various human cancers, especially slow growing, **refractile cancers** for which there are no therapies. Thus, "refractile cancers" are being treated with salinosporamides not "refractile mammalian cancer cell".

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The recitation of "one additional anti-neoplastic agent" in claim 9 renders the claim indefinite because neither claim 9 nor claim 7 on which it is dependent states that the pharmaceutical composition comprises a first anti-neoplastic agent.

2. The recitation of "one additional anti-neoplastic agent" in claim 23 renders the claim indefinite because neither claim 23 nor claim 10 on which it is dependent states that the pharmaceutical composition comprises a first anti-neoplastic agent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

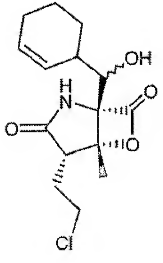
The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 4 to 7, 24 and 25 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Fenical et al. (WO 2002/047610), cited by Applicants.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The reference discloses that Salinosporamide A was isolated and obtained in pure form. Note the description of Figure 1 on page 5, lines 9-16 and the structure of Salinosporamide A shown below:

Figure 1. Structure of salinosporamide A, the first novel, bioactive metabolite obtained from the *Salinospora* group. The isolation of this compound proves that the *Salinospora* group is a resource for unique, biologically active metabolites. The producing strain was cultured in a seawater-based medium and the compound was obtained in pure form following a series of chromatographic steps. The structure of salinosporamide A was elucidated using 1D and 2D nuclear magnetic resonance and high resolution mass spectral data analyses.



This compound corresponds to the claimed compound of the structure (I) wherein E_1, E_3, and E_4 are O; R_1 is chlorinated alkyl; R_2 is methyl; R_3 is hydroxyl; E_2 is –NH-; and x

is 0. The reference also discloses Salinosporamide A in a pharmaceutical composition. Note Examples 1-15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

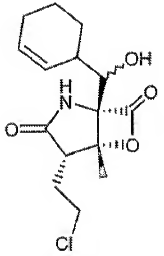
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9 to 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fenical et al. (WO 2002/047610) in view of Wu et al. (WO 1999/022729), cited and Dick et al. (Journal of Biological Chemistry, 271(13), 7273-7276, 1996, cited by Applicants and Ogiso et al. (Cancer Research, 60, 2429-2434, 2000), cited .

Determination of the scope and content of the prior art (MPEP §2141.01)

Fenical et al. disclose that Salinosporamide A was isolated and obtained in pure form. Note the description of Figure 1 on page 5, lines 9-16 and the structure of Salinosporamide A shown below:

Figure 1. Structure of salinosporamide A, the first novel, bioactive metabolite obtained from the *Salinospora* group. The isolation of this compound proves that the *Salinospora* group is a resource for unique, biologically active metabolites. The producing strain was cultured in a seawater-based medium and the compound was obtained in pure form following a series of chromatographic steps. The structure of salinosporamide A was elucidated using 1D and 2D nuclear magnetic resonance and high resolution mass spectral data analyses.



This compound corresponds to the claimed compound of the structure (I) wherein E_1, E_3, and E_4 are O; R_1 is chlorinated alkyl; R_2 is methyl; R_3 is hydroxyl; E_2 is –NH-; and x is 0. The reference also discloses Salinosporamide A in a pharmaceutical composition. Note Examples 1-15. Fenical et al. also disclose that Salinosporamide A, a biomolecule produced by growth of a strain of actinomycete, is an anti-cancer agent. See claim 6, for example.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Fenical et al. do not disclose that Salinosporamide A can be combined with at least one additional anti-neoplastic agent or that it could be used to treat refractile mammalian cancer cell.

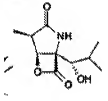
Finding of prima facie obviousness---rational and motivation (MPEP §2142-2413)

Wu et al. disclose that proteasome inhibitors, such as lactocystin and analogues thereof can be used for treating cancer and can be used in combination with other pharmaceutical agents. See the paragraph spanning pages 45-46 reproduced below. LAC is the abbreviation for lactacystin.

> It is an embodiment of this invention to have identified known immunosupressive drugs including rapamycin, FK506 and cyclosporin A as inhibitors of enhanced proteasome activity. It is therefore a specific embodiment of this invention for providing these immunosupressive drugs of a pharmaceutically effective amount and in combination with specific proteasome inhibitors of a pharmaceutically effective amount, as an example but not limited to LAC or its analogues to achieve an additive effect in blocking cell proliferation and any other relevant cell function. Such combinations as described can be used but are not limited to the treatment of cancer, graft rejection and autoimmune diseases.

Dick et al. disclose that clasto-lactacystin β-lactone is the active intermediate lactacystin analog that interacts with the proteasome and is produced in aqueous solution at pH 8 (Dick, Abstract). The structure of clasto-lactacystin β-lactone is shown in Scheme 1 on page 7274. See its structure below.

β-lactone



Ogiso et al. disclose that "the stress-induced etoposide resistance was effectively prevented in vitro by the proteasome inhibitor lactacystin in both intrinsically resistant and sensitive tumor cells (colon cancer HT-29 and ovarian cancer A2780 cells, respectively). Furthermore, lactacystin effectively enhanced the antitumor activity of etoposide in the refractory HT-29 xenograft cells. These results indicate that lactacystin could serve as a new therapeutic agent to circumvent resistance to topo II-targeted chemotherapy in solid tumors."

It would have been obvious to one of ordinary skill in the art to use Salinosporamide A which is structurally similar to clasto-lactacystin β-lactone for the treatment of refractory or refractile cancer cells since the prior art teaches that lactacystin and analogs thereof are proteasome inhibitors that can be used to treat cancer. Since it is known in the prior art that lactocystin enhances the antitumor effect of the antitumor drug etoposide, it would have been obvious to make a pharmaceutical composition comprising Salinosporamide A and an additional anti-neoplastic agent.

The claimed pharmaceutical composition and method of treating refractile mammaian cancer cell would have been rendered obvious by the teachings of the references in the absence of any unobvious or unexpected property or result.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10 to 23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. **11/996,801**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the indiscriminate selection of "some" among "many" is prima facie obvious. See In re Lemin, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity. The purified compounds of the copending application are equivalent to the claimed isolated compounds having the structure (I) because a compound must be isolated in order to be purified.

One of ordinary skill in the art would thus be motivated to make the claimed compounds which are embraced by the prior art in order to obtain additional beneficial products which would be useful for the same purpose. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instantly claimed invention would have been rendered obvious to one skilled in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 4-7, 24 and 25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. **12/638,860**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the indiscriminate selection of "some" among "many" is prima facie obvious. See In re Lemin, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity. The purified compounds of the copending application are equivalent to the claimed isolated compounds having the structure (I) because a compound must be isolated in order to be purified.

One of ordinary skill in the art would thus be motivated to make the claimed compounds which are embraced by the prior art in order to obtain additional beneficial products which would be useful for the same purpose. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instantly claimed invention would have been rendered obvious to one skilled in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 4 to 7, 9, 24 and 25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 to 15 of U.S. Patent No. **7,176,232** and claims 1 to 4 of U.S. Patent No. **7,928,138**. Although the conflicting claims are not identical, they are not patentably distinct from each other

because the indiscriminate selection of "some" among "many" is prima facie obvious. See In re Lemin, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity.

One of ordinary skill in the art would thus be motivated to make the claimed compounds which are embraced by the prior art in order to obtain additional beneficial products which would be useful for the same purpose. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instantly claimed invention would have been rendered obvious to one skilled in the art.

. Claims 10 to 23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 to 3 of U.S. Patent No. **7,176,233** and claims 1 to 27 of U.S. Patent No. **7,635,712**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the indiscriminate selection of "some" among "many" is prima facie obvious. See In re Lemin, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity.

One of ordinary skill in the art would thus be motivated to make the claimed compounds which are embraced by the prior art in order to obtain additional beneficial products which would be useful for the same purpose. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instantly claimed

invention would have been rendered obvious to one skilled in the art.

Claim 9 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 to 15 of U.S. Patent No. **7,179,834** . Although the conflicting claims are not identical, they are not patentably distinct from each other because the indiscriminate selection of "some" among "many" is prima facie obvious. See In re Lemin, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity.

One of ordinary skill in the art would thus be motivated to make the claimed compounds which are embraced by the prior art in order to obtain additional beneficial products which would be useful for the same purpose. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instantly claimed invention would have been rendered obvious to one skilled in the art.

Response to Arguments

The Pallidino Declaration under 37 CFR 1.132 filed June 9, 2011 is sufficient to overcome the rejection of claims 10 to 13 based upon 35 U.S.C. 112, first paragraph.

The rejection of the claims under 35 U.S.C. 112, second paragraph presented in the previous Office action is withdrawn due to Applicants amendment of the claims.

With respect to the double patenting rejections, Applicants request that the Examiner hold the rejections in abeyance until the present application is in condition for allowance in order to reassess any alleged claim overlap. As no terminal disclaimers have been filed the double patenting rejections are maintained.

Allowable Subject Matter

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FIONA T. POWERS whose telephone number is (571)272-0702. The examiner can normally be reached on Mon - Thurs 6:15 am - 2:45 pm (in the office) and Fri 7:00 am - 5:30 pm (telework day).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/FIONA T POWERS/
Primary Examiner, Art Unit 1626

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August 23, 2011